

Annual Reporting Form for SCEDDBO Projects and Cores

Administrative Core

Period covered by the report: 5/1/2008 – 4/30/2009

EPA Agreement Number: RD83329301-0

Investigators: Marie Lynn Miranda, Richard Auten, Sherman James, Pamela Maxson

Project Period: Year 2

Objectives of Core

The Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) is governed through an Administrative Core that includes an Executive Committee composed of the Director, the two Co-Directors, and the Project Manager; an Internal Steering Committee composed of members of the Executive Committee and the Directors of the Research Projects and the Facility and Community Outreach Cores; and an External Advisory Committee composed of senior environmental health scientists, as well as community representatives, with expertise relevant to SCEDDBO, who provide informal consultation, as well as annual formal evaluation of Center research and outreach activities.

The specific aims of the Administrative Core are to:

- a. Provide scientific direction and leadership;
- b. Coordinate and foster interactions among research project and facility core investigators;
- c. Provide administrative services for the Center;
- d. Direct the Young Investigators program; and
- e. Represent Duke's SCEDDBO to the university, the community, the NIH, other Children's Environmental Health Centers across the United States, and the policy and scientific community interested in children's environmental health more broadly.

In all activities, SCEDDBO emphasizes the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social, and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators are all indicative of the importance that we place on fostering environments where all people can prosper.

Progress Report/Summary of Accomplishments

Dissemination. SCEDDBO offered a well-attended mini-symposium at the EPA in the Research Triangle Park in January 2009. This symposium was designed to present EPA employees with a synopsis of the work that SCEDDBO does, emphasizing the environmental contributors to disparities in birth outcomes. This was an excellent opportunity for discussion and feedback.

Dr. Miranda also represented the scientific mission of SCEDDBO as part of the USEPA's BOSC review of the agency's human health research program in January 2009. Specifically, Dr. Miranda co-authored and presented with Ms. Devon Payne Sturges (USEPA) a poster regarding Long Term Goal 3 entitled "Differential Vulnerability to Environmental Contaminants and Adverse Outcomes during Early Childhood." This poster was well-received and SCEDDBO was commented on very favorably by the BOSC review panel in its written report.

Dr. Miranda also brought her perspective on geospatial analysis and its usefulness in assessing and analyzing public health issues via her participation in the US Centers for Disease Control

and Prevention's Geospatial Science and Healthy Communities Expert Panel, held in Atlanta, GA, in May 2008.

New Collaborations. As part of our mission to both support the work of young investigators and advance the research mission of SCEDDBO, we began new collaborations with Dr. Staci Bilbo, Assistant Professor, Department of Psychology and Neuroscience, Duke University and Dr. Rebecca Fry, Assistant Professor, Gillings Global School of Public Health, UNC. We are working with Dr. Bilbo on new mouse models to explore the joint impact of environmental and social stressors on birth and developmental outcomes. We are working with Dr. Fry to explore gene expression and epigenetic changes associated with *in utero* metals exposures, with a particular emphasis on cadmium. In both cases, we are working with these new investigators to develop grant applications for submission to NIH and the EPA. In addition, we established a CDC-funded collaboration with Dr. Heather Stapleton, Assistant Professor, Nicholas School of the Environment, Duke University. This study leverages our ongoing clinical obstetrics project to assess *in utero* exposures to brominated flame retardants, as well as the relationship between brominated flame retardant body burden and maternal thyroid function.

Research Project A: Mapping Disparities in Birth Outcomes

Period covered by the report: 5/1/2008 – 4/30/2009

EPA Agreement Number: RD83329301-0

Investigators: Marie Lynn Miranda (PI), Alan Gelfand, Sherman James, Pamela Maxson, Geeta Swamy

Project Period: Year 2

Objectives of Research

Project A utilizes the conceptual framework of the “weathering hypothesis,” which posits that chronic and persistent stressors lead to accelerated biological aging of women, which in turn accounts for adverse birth outcomes among certain subpopulations. The central objective is to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in fetal growth restriction.

Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims are to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than percentile cut points; and
3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

This project evaluates a large number of factors in diverse populations, providing broad relevance for birth outcomes across time, space, and demography. Identifying social and environmental factors contributing to fetal growth restriction will improve our understanding of disease etiology and explain the racial disparity in disease incidence, leading to effective interventions against poor outcomes in all population groups.

Progress Report/Summary of Accomplishments

Over the past year, the Project A research team has met both at full group level and in small groups to discuss new research ideas, review progress of current analysis and identify next steps, and work on manuscript preparation.

We have completed considerable methodological work on expected performance accruing to *synthesizing categorical datasets* with the objective of enhancing inference. We are particularly interested in how to deal with a collection of datasets of varying sizes that are all relevant to a particular scientific question, but which include different subsets of the relevant variables, with some overlap. This work attempts to synthesize cross-classified categorical datasets drawn from a common population where many of the sets are incomplete (i.e., one or more of the classification variables is unobserved), but at least one is completely observed. This is expected to reduce uncertainty about the cell probabilities in the associated multi-way contingency table as well as for derived quantities such as relative risks and odds ratios. We have made substantial progress on the underlying modeling and have developed a simulation example as well. We have also addressed the issue of the complete dataset not being a random sample from the population, as would be typical in practice. A manuscript on this work is presently in submission.

Out of efforts to develop new spatial methodologies for addressing health disparities, additional methodological work on *disaggregated spatial modeling for areal unit categorical data* is currently underway. This work uses innovative statistical methodology that extends spatial disease mapping techniques to model subgroups within areal units using a spatially smoothed, multilevel loglinear model. This work is forthcoming in the *Journal of the Royal Statistical Society, Series C*. We are also exploring the public health applications of this methodology to elucidate health disparities across space and subgroups.

We have spent considerable time linking the detailed birth record data to USEPA PM₁₀, PM_{2.5}, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birthweight. We are especially focused on refining exposure metrics to most effectively characterize meaningful exposures, as well as to capture any windows of vulnerability. Significant progress has been made on the relationship between birth outcomes and exposure to particulate matter and ozone separately, and the current focus is determining how to characterize joint exposure to both particulate matter and ozone. A manuscript on this work is currently in submission.

Related work has studied the use of a PM_{2.5} exposure simulator to explain birthweight. In a recently submitted paper, a template is developed for using an *environmental dose simulator* to connect ambient exposure to personal exposure. Then, using various exposure metrics, calculated from these personal exposures that are clinically plausible over the course of a pregnancy, linkage is built to adverse birth outcomes.

Our project on *racial residential segregation* has now seen the near completion of one paper (currently in preparation) which enables quantification of racial exposure/isolation at finer spatial scales within SMSA's. Such a measure can be connected to measures of social and economic disadvantage at these scales to gain insight into how racial residential segregation has manifested itself across urban landscapes. In turn, this promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes. Although our initial efforts were statewide, we have since decided that, given the significantly more detailed data available for Durham County, we will focus on this area while we work to determine what variables are most important to characterizing racial residential segregation in terms of its health consequences.

Recent work has focused on building *spatial downscalers*. Such modeling strategies enable the fusion of monitoring station data with computer model output to better assess environmental exposure at point level spatial resolution. Such downscalers can be dynamic, enabling the tracking of exposure through time. With improved estimation of local exposure, we can better examine linkage between exposure and adverse birth outcomes. A first paper on this methodology is forthcoming. Current work is developing extensions to fusion for exposure to multiple contaminants as well as to account for modeling error in the computer model output. Another recently completed manuscript (currently in submission) builds *joint models for birthweight and gestational age* using bivariate normal mixtures. Such joint modeling adjusts for maternal risk factors and provides mixture analysis of the residuals to help illuminate further subpopulations with differential risk for adverse joint birth outcomes. Modeling of the mixture components is done through gestational age and then birthweight given gestational age. Joint modeling eliminates potential causal inference concerns.

We have also submitted a review article on social and environmental contributors to disparities in birth outcomes based on both national and North Carolina data, as a way of compiling the many literatures we have accessed throughout our work on Project A.

In addition, we have been working on specific analysis and manuscripts examining the impact of maternal age and birth order on birth weight (manuscript in submission), on modeling ordinal categorical data using Gaussian processes (manuscript in preparation), and the etiology of racial disparities in maternal hypertensive disorders (manuscript in submission). We have also developed new spatial data layers on road intensity and measures of the built environment for use in upcoming analyses.

Future Activities

We recently began the process of linking participants in Project B with their associated birth certificate record. We are excited to begin exploring the additional insights into the detailed birth record data that can be gleaned by linking these data with the rich dataset collected in Project B. This linkage will not only allow us to explore issues of data accuracy in the detailed birth record, but will also allow us to begin implementing the methods of synthesizing categorical data discussed above.

Publications

Miranda, ML, Maxson, P, Kim DK. Early Childhood Lead Exposure and Exceptionality Designations for Students. Forthcoming, *International Journal of Child and Adolescent Health*.

Tassone, E, Miranda, ML, Gelfand, A. Disaggregated Spatial modeling for Areal Unit Categorical Data. Forthcoming, *Journal of the Royal Statistical Society*.

Berrocal, V, Gelfand, A, Holland, D. A Spatio-temporal Downscaler for Output from Numerical Models. Forthcoming, *Journal of Agricultural Biological and Environmental Sciences*.

Berrocal, V, Miranda, ML, Gelfand, A, Bhattacharya, S. Synthesizing Categorical Data to Enhance Inference. In submission.

Berrocal, V, Gelfand, A, Holland, D. Joint Data Assimilation for Ozone and PM 2.5 – a Bivariate Space-Time Downscaler under Misalignment. In submission.

Berrocal, V, Burke, JM, Gelfand, A, Holland, D, and Miranda, ML. On the use of a $PM_{2.5}$ simulator to explain birthweight. In submission.

Anthopolos, R, Gelfand, A, James, S, Miranda, ML. A Neighborhood Level Spatial Measure of Racial Residential Isolation for Health Disparities Research. In preparation.

Swamy, GK, Edwards, S, Gelfand, A, James, SA, Miranda ML. Maternal Age, Birth Order, and Race: Differential Effects on Birthweight. In submission.

Miranda, ML, Maxson, P, Edwards, S, Swamy, GK, Gelfand, A, James, SA. Disparities in Maternal Hypertension and Pregnancy Outcomes: Evidence from North Carolina, 1994-2003. In submission.

Gray, S, Edwards, S, and Miranda, ML. Assessing exposure metrics for PM and birthweight models. In submission.

Schwartz, SL, Gelfand, A, and Miranda, ML. Joint distribution of birthweight and gestational age using mixture models. In submission.

Miranda, ML, Maxson, P, Edwards, S. Social, Environmental, and Host Factor Contributions to Disparities in Pregnancy Outcomes. In submission.

Supplemental Keywords

Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation

Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes

Period covered by the report: 5/1/2008 – 4/30/2009

EPA Agreement Number: RD83329301-0

Investigators: Redford Williams (PI), Allison Ashley-Koch, Richard Auten, Christina Gibson-Davis, Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy,

Project Period: Year 2

Objectives of Research

The central objective of the Healthy Pregnancy, Healthy Baby Study is to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There are four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
 - a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
 - b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and
 - c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

Progress Report/Summary of Accomplishments

As of 4/30/09, 1390 women have been enrolled in the study, with only 128 women withdrawn or lost to follow-up. Women are recruited from Duke University Medical Center (DUMC) and Lincoln Community Health Center. Demographic data indicate that we are successfully recruiting women who are most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women.

The following information is collected from participants in the Healthy Pregnancy, Healthy Baby Study:

- Psychosocial measures include: CES-D, perceived stress, self-efficacy, interpersonal support, paternal support, perceived racism, perceived community standing, pregnancy intention, John Henryism Active Coping Scale, NEO Five Factor Inventory of personality.
- Environmental exposure survey measures include: short survey on fish consumption, smoking pattern and exposure to second-hand smoke, and drinking water source.

- Maternal and neonatal medical record abstraction includes: detailed pre-pregnancy medical and social history, antepartum complications, birth outcomes, and neonatal complications.
- Blood samples for genetic and environmental analysis to assess candidate genes related to environmental contaminant (nicotine, cotinine, cadmium, lead, mercury, arsenic, and manganese) metabolism, inflammation, vascular dysfunction, and stress response.
- Cord blood and placental samples are currently being stored for future genetic analysis and evaluation of activity at the maternal-fetal interface.

We have been highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 485 delivery samples collected.

All maternal data is georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Health Baby Study also includes an in-depth neighborhood assessment designed to capture both built environment and community-level social stressors and community resources. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

To date, we have generated genotypes on approximately 1000 blood samples from pregnant women for 104 Single Nucleotide Polymorphisms (SNPs) in sixteen genes. Candidate genes include those involving human environmental contaminant clearance (heavy metals and environmental tobacco smoke), infection and inflammation (cytokines, chemokines, and bacterial pathogen recognition), maternal stress response (serotonin), and other pathways that have been implicated as potential drivers of health disparities (vascular responsivity). Genotyping will continue in year 3, as our currently proposed candidate list includes approximately 50 different genes.

Statistical analysis regarding candidate gene polymorphisms began in June 2008 and is ongoing. Preliminary genetic analyses are described below.

The ***Vitamin D receptor gene (VDR)*** has a wide variety of functions, including calcium homeostasis and modulating circulating levels. Subtle genetic variation has also been linked to adverse conditions including diabetes, cancer, renal disease, and autoimmune disorders. In multivariable regression modeling, we found a significant association between the VDR variant (rs731236, a coding, synonymous SNP) and preterm birth ($p=0.04$) for non-Hispanic black (NHB) women in our study population. The odds of having an infant born preterm were 2.9 times higher for women with the CC genotype at this marker compared with women with the TT genotype ($p=0.04$) and were 3.8 times higher for women with the CC genotype compared with women with the CT genotype ($p=0.01$). This same association did not hold true among the non-Hispanic white (NHW) women. Furthermore, in addition to 6 other SNPs within the VDR gene, rs731236 was also associated with infant birthweight among NHB but not NHW women. Such analyses exemplify how genetic variation may contribute to racial differences in health outcomes.

Ongoing statistical analysis includes genes encoding G-protein coupled receptor kinases (GRK) which have been linked to racial differences in vascular responsivity. Specifically, polymorphisms in the GRK-5 gene have demonstrated a pharmacogenomic interaction among African Americans in the setting of cardiovascular disease and response to β -adrenergic receptor (β AR) blockade, which is standard therapy for cardiac failure and ischemia.

Psychosocial Indicators. Preliminary analyses have been completed on psychosocial influences on birth outcomes. Pregnancy intention is an important indicator of behavior and psychological health during pregnancy. We continue to investigate the influences intention and psychosocial health have on birth outcomes. This work was presented at the UNC Women's Health Research Day as well as at a Perinatal Health Committee meeting at the NC legislature. A draft manuscript is in progress and will be ready for submission early in year 3. Additionally, work has begun examining the influences of psychosocial health and smoking status.

Future Activities

In the upcoming year, we will continue to enroll study participants with our new target sample size of 1800 pregnant women. Based on analyses of the preliminary data, we are considering extending our target sample size to 2000 women to ensure full statistical powering for the many subgroup analyses we have planned.

We will continue analyses on approximately 1000 participants with complete pregnancy data, genetic results, and environmental results. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity.

Supplemental Keywords

Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms

Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Period covered by the report: 5/1/2008 – 4/30/2009

Date of report: 7/1/2009

EPA Agreement Number: RD83329301-0

Investigators: P.I.: Richard L. Auten, Co-Inv: W. Michael Foster

Project Period: Year 2

Objectives of Research: Specific Aims

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure 're-programs' maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

Progress Report/Summary of Accomplishments

1. We have submitted a manuscript (in revision) that reports the effect of prenatal diesel particulate pulmonary exposure on postnatal ozone induced airway hyperreactivity. Our report shows: dose-dependent effects of particulate matter inhalation on maternal inflammatory responses; synergistic effects of prenatal diesel exposure and postnatal ozone exposure on lung inflammatory cytokine responses, synergistic effects of prenatal diesel and postnatal ozone on postnatal airway hyperresponsiveness to inhaled methacholine challenge.
2. We have expanded these studies by using prenatal exposures to spontaneous inhalation of fresh diesel generated by internal combustion automobile engines in collaboration with Dr. Ian Gilmour, US-EPA. As with the instilled particulate matter (St. Louis particle, NIST+1648), pups born to dams exposed to environmentally relevant concentrations (2 mg/m³) of fresh diesel exhaust had worse ozone-induced airway hyperresponsiveness than those born to control-exposed dams. We found this effect was concentration dependent, with the effects of exposure to 2.0 mg/m³ more severe than exposure to 0.5 mg/m³. Importantly, the prenatal exposure to diesel exhaust combined with postnatal/perinatal ozone exposure led to persistence of airway hyperresponsiveness in adult mice even after stopping exposures for 4 weeks. These findings were presented at the 2009 Pediatric Academic Societies annual meeting in Baltimore. This implies that the perinatal exposure effects may have permanent health effects that persist to adulthood. We are trying to determine if the persistent vulnerability to increased responsiveness to methacholine challenge is attributable to altered afferent innervation, as suggested in some recent reports. So far, studies conducted in animals subjected to cervical vagotomy have not shown alterations in methacholine responsiveness, which would suggest that the altered phenotype may be due to alterations in smooth muscle

responsiveness or altered efferent signaling. A second manuscript is in preparation to describe these findings.

3. We are currently analyzing placental inflammatory mediators from fetuses carried by diesel and particulate matter exposed mice obtained at E18 (full-term: 20-21 days).
4. We have conducted preliminary studies that restrict nesting/housing resources during pregnancy as a model of non-chemical stressor exacerbations of chemically impaired perinatal toxicity. Our preliminary findings have shown that deprivation during pregnancy adds to the adverse effect of nesting restriction (housing deprivation) on postnatal weight gain during the immediate postnatal period.

Future Activities

1. We are presently conducting studies of combined pre and postnatal air pollutant exposure (diesel, ozone) in mouse strains with genetic susceptibility to and resistance to ozone-induced airway hyperresponsiveness to determine the genetic contribution to the synergistic effects of prenatal maternal inflammation with postnatal ozone-induced airway hyperresponsiveness. Preliminary studies conducted with ozone exposed neonatal mice lacking the gene *NQO1* (NAD(P)H quinone oxidoreductase) suggest that this component of the inflammatory response cascade is important to ozone-induced airway hyperresponsiveness. These findings were presented at the 2009 annual American Thoracic Society International Conference at San Diego.

Publications

1. **Auten RL**, Mason SN, Potts EN, Fischer BM, Huang Y, Foster WM. Maternal exposure to particulate matter increases postnatal ozone-induced airway hyperreactivity in juvenile mice. In submission.

Supplemental Keywords

Airway hyperreactivity, diesel exhaust particles, air pollution, lung function